

EDITORIAL COMMENT

C-Reactive Protein and Cardiac Allograft Vasculopathy: Is Inflammation the Critical Link?*

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“And it appears to me that one ought also know what diseases arise in man from the powers and what from the structures. What do I mean by this? By powers, I mean intense and strong juices; and by structures, whatever conformations there are in man.”

—Hippocrates (1)

Offering an insightful hypothesis, Hippocrates correctly surmised the importance of dynamic circulatory factors in mediating illness. The search for these elusive “intense and strong juices” has led us into a fascinating journey of discovery of inflammatory markers in cardiovascular medicine. More precisely, the significance of systemic and local inflammation in determining the development and behavior of atherosclerosis has been the subject of intense scrutiny (2). Many years ago, Virchow championed the inflammatory theory of atherosclerosis and referred to it as “endarteritis deformans” (3). By this he meant that the atheroma, initiated by mechanical injury, was a product of inflam-

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mation within the intima and that fibrous thickening evolved as a reactive consequence by proliferating connective tissue cells. Contemporary thoughts have continued to advocate the inflammatory theory of atheroma mediation, and as Ross reaffirmed, “atherosclerosis is clearly an inflammatory disease and does not result simply from the accumulation of lipids” (4). In this issue of the *Journal*, Hognestad et al. (5) report yet another study that demonstrates an association between elevated concentrations of plasma C-reactive protein and allograft atherosclerosis in heart transplant recipients. Furthermore, these authors determined that pravastatin 20 mg/day for six weeks reduced plasma C-reactive protein levels independent of changes in the lipid profile. These data confirm previous observations on the association of plasma C-reactive protein, graft failure, and cardiac allograft vasculopathy (6–8) and, although very preliminary, support the concept that statin

therapy might improve outcomes in cardiac transplantation by lipid-independent, anti-inflammatory properties.

Cardiac allograft vasculopathy. Cardiac allograft vasculopathy is a unique form of accelerated atherosclerosis of the allograft and remains the leading cause of late mortality in patients who survive the first year post transplantation (9). Although its pathogenesis is not fully elucidated, it seems that cardiac allograft vasculopathy is associated with an injury of the coronary vessel endothelium of the transplanted heart, initiated by a variety of immunologic factors (acute rejection, immunosuppressive therapy, human leukocyte antigen mismatches, cytomegalovirus infection) and propagated by non-immunologic mechanisms (donor age, lipids, obesity) that result in the development of the characteristic intimal hyperplasia that is the hallmark of this disease (10–12).

Initial observations demonstrated that only the vessels of the allograft were involved in this form of accelerated atherosclerosis, suggesting immunologic mechanisms as the main underlying factor in the development of this disease (13). However, despite the successful use of immunosuppressive agents and control of rejection, cardiac allograft vasculopathy still occurs and gives credence to the hypothesis that other nonimmune risk factors acting in concert with immunologic risk factors are implicated in the development of allograft vasculopathy (10–12). Thus, the recognition that rejection-independent events could influence the development of cardiac allograft vasculopathy became obvious through investigations that pointed to the role of ischemia-reperfusion injury surrounding engraftment, the contribution of advanced donor age, mode of brain death, aberrances within the microvasculature, and metabolic derangements including hyperlipidemia (10,12,14,15). Indeed, a recent experimental study demonstrated that allograft vasculopathy could also develop without a cellular alloimmune response (16).

Inflammation in heart transplantation: immunologic or non-immunologic? The evidence that inflammation may be a central event in cardiac allograft vasculopathy and graft failure, independent of acute allograft rejection, is gaining acceptance. Several investigations have indicated that early events that surround engraftment and exemplify inflammatory processes are closely linked with the genesis of cardiac allograft vasculopathy. In this regard, investigations have linked the up-regulation of pro-inflammatory cytokines, markers of diffuse microvascular dysfunction, and procoagulant proteins with graft failure as a result of allograft vasculopathy (17). Another study by Fyfe et al. (18) demonstrated that serum amyloid-A, another acute-phase protein, was significantly elevated in cardiac transplant recipients with allograft vasculopathy. Thus, the consistent finding of elevated C-reactive protein levels in cardiac transplantation, along with the demonstration that this is predictive not only of cardiac allograft vasculopathy but also of allograft failure, provides another strong step in answer-

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ing the importance of the deleterious effects of low-grade inflammation in this unique disorder (5–8). Most available data point to the presence of systemic inflammation without detectable evidence of immunologically mediated allograft rejection in cardiac transplantation.

C-reactive protein, atherosclerosis, and cardiac allograft vasculopathy. C-reactive protein, a sensitive marker of systemic inflammation, is produced by hepatocytes and reflects amplification of cytokine activation (19). Recently, several investigators have shown that C-reactive protein is an important risk factor for atherosclerosis, coronary artery disease, and vascular events (2). An increase in plasma levels of C-reactive protein predicts subsequent cardiovascular events in healthy men (20) and women (21), patients with unstable and stable angina (22–24), and those with a history of myocardial infarction (25).

The relationship between plasma C-reactive protein and cardiac allograft vasculopathy has come to the forefront in recent years. First, Eisenberg et al. (7) demonstrated that plasma levels of C-reactive protein correlated with the frequency of grade III acute rejection and predicted allograft failure. In another study by Pethig et al. (6) plasma C-reactive protein levels were significantly higher in 102 cardiac transplant recipients who had progression of cardiac allograft vasculopathy by serial coronary angiography. More recently, Labarrere et al. (8) offered insight into both the role of C-reactive protein and the underlying mechanism by which it could contribute to the development of cardiac allograft vasculopathy. The authors prospectively studied 109 patients in the first three months after cardiac transplantation to investigate the relationship between plasma C-reactive protein, endomyocardial biopsy findings, intercellular adhesion molecule 1 (ICAM-1) concentrations, and clinical outcome. During follow-up, the development and severity of cardiac allograft vasculopathy was significantly higher in patients with higher C-reactive protein levels. In addition, the authors demonstrated that C-reactive protein was closely associated with the expression of endothelial ICAM-1 and suggested that C-reactive protein could represent a peripheral marker of allograft inflammation. Furthermore, an investigation of different immunosuppressive strategies has indicated that C-reactive protein is unaffected either by the type of immunoprophylaxis employed or by their effects on allograft rejection (26). The study reported by Hognestad et al. (5) herein, although observational and cross-sectional in design, confirms that plasma levels of C-reactive protein are associated with the development of cardiac allograft vasculopathy. In addition, in 49 cardiac transplant recipients, plasma C-reactive protein was measured at six months after transplantation and compared with a measurement at late follow-up demonstrating that patients who developed allograft vasculopathy had a more significant increase in C-reactive protein than patients who did not develop allograft vasculopathy.

The crucial question that begs an answer is whether these findings establish C-reactive protein as a risk factor or

merely a risk marker. The predominant measurement of this inflammatory marker was performed late after transplantation (five years), indicating that systemic inflammation tends to persist throughout the course of transplantation. Although a retrospective sample at baseline was evaluated in a smaller subset, this information cannot be construed to establish the cause-and-effect relationship, because adverse allograft outcomes <5 years are left unaccounted. Also, the gold standard used for the diagnosis of cardiac allograft vasculopathy is imprecise, and it is conceivable that the diagnostic accuracy of C-reactive protein could have been further enhanced had intravascular ultrasound been used for the detection of cardiac allograft vasculopathy (11). Therefore, these data are best interpreted as indicating that C-reactive protein is a “marker”—not a “factor”—in arbitrating cardiac allograft vasculopathy.

C-reactive protein and statins: a therapeutic target in heart transplantation? Statins inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate; statins also reduce the downstream products of mevalonate in the cholesterol synthesis pathway. Two of these downstream products, farnesyl pyrophosphate and geranylgeranyl pyrophosphate, are the moieties that can modulate the function of certain essential signaling proteins that account for anti-inflammatory properties (27). Accumulating more evidence for an anti-inflammatory effect of statins independent of their lipid-lowering effect, Jialal et al. (28) have also previously demonstrated that simvastatin, pravastatin, and atorvastatin decrease high sensitivity C-reactive protein, indicating that this is probably a class effect. The demonstration that statin therapy improves outcomes after heart transplantation independent of lipid lowering has now been well accepted (29,30). The suggestion that pravastatin reduces C-reactive protein in cardiac transplantation provides further support that statins exert their beneficial effects on cardiac allograft vasculopathy by the reduction of inflammation (5). A recent investigation conducted for primary and secondary prevention of coronary artery disease indicated that pravastatin was associated with a 13% decrease in C-reactive protein levels (31). Yet, the study by Hognestad et al. (5) suggested a 25% decline in C-reactive protein levels. Why is this so? It is known that a synergistic association between statins and cyclosporine yields incremental anti-inflammatory effects. Thus, Katznelson et al. (32) have shown that pravastatin and cyclosporine act synergistically to reduce cytotoxic T lymphocyte activity, suggesting that this specific effect is quite unique to transplant recipients. Despite all these steps in the right direction, evidence that the C-reactive protein lowering effect influences survival of the allograft is lacking. The small sample on the effects of pravastatin on C-reactive protein reported in the current study should be a hypothesis generating finding to spur further study.

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